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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,852	GAZIT, EHUD	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12,40,72,73,75-79,81-96,99-102,118,141,148,155-159 and 163* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12,72,77-79,81,95 and 163* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/09;5/11/09;5/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix -SCORE*.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 40,73,75,76,82-94,96,99-102,118,141,148 and 155-159.

DETAILED ACTION

Status of Claims

1. The amendments filed on 28 May 2009 have been entered into the record and have been fully considered. Claims 1, 12, 72, 81, 95, and 163 are amended. New claim 163 is added. Claims 74, 97 and 98 are cancelled.

2. Claims 1, 12, 72, 74, 77-79, 81, 95 and 163, drawn to a synthetic or recombinant peptide, a pharmaceutical composition comprising the peptide thereof, comprising an amino acid sequence X-Y or Y-X, wherein X is an aromatic amino acid and Y is a beta-breaker amino acid, are under consideration in the instant application.

3. New grounds of objection and rejection are as follows.

Response to Amendment

Withdrawn rejections

4. The rejection of claims 1, 12, 72, 74, 77-79, 81 and 95 under 35 U.S.C. 101 is withdrawn, because of the amendment of the claims to recite "synthetic or recombinant".

5. The rejection of claims 72, 74, 77-79, 81 95 and 97, under 35 U.S.C. 112, first paragraph, scope of enablement is withdrawn, because of

amendment of the claims to cancel the limitations directed to prevention and treatment.

6. The rejection of claims 1, 12, 72, 74, 77-79, under 35 U.S.C. 112, second paragraph is withdrawn, because of the amendment of relevant claims and Applicant's persuasive argument.

7. The rejection of claims 1, 12, 72, 74, 77-79, 95 and 97, under obviousness double patenting is withdrawn, because of the submission of a terminal disclaimer.

8. The rejection of claims 1, 72, 74, and 77-79 under 35 U.S.C. 102, is withdrawn, because of amendment of claims directed to a dipeptide only.

Objection maintained

9. Claim objection

The objection of claims 12 and 81 is applied to the amended claims 12 and 81 and new claim 163 for reasons of record in the Office Action dated 16 December 2008.

10. Applicant argues that the non-elected **species** can be rejoined, in case SEQ ID NO: 121 (elected invention) is found to be patentable (emphasis added). Applicant's argument is considered, however, is not persuasive because as per the restriction requirement dated 4 June 2008, each of the peptide molecules was placed in different **inventive groups and not species**. It is therefore, reiterated that claims 12, 81 and 163 are

objected as these recite non-elected inventions. Appropriate correction is required.

New Rejections

Claim Rejections - 35 USC § 112, first paragraph- Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 72, 77-79, 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

12. Claims 1, 72, 74, 77-79 and 95, drawn to a synthetic or recombinant peptide, a pharmaceutical composition comprising the peptide thereof, comprising an amino acid sequence X-Y or Y-X, wherein X is an aromatic amino acid and Y is a beta-breaker amino acid. The claims further recite that 'Y' is a synthetic Cα-methylated amino acid or α-aminoisobutyric acid (Aib), and is a β-sheet breaker amino acid.

Please note that the claims broadly read on any dipeptide, wherein X is any aromatic amino acid that can be L or D stereoisomer and Y is any beta breaker amino acid.

13. The specification teaches that synthetic peptides function as β-sheet breakers to disrupt the β-pleated sheets and inhibit the formation of amyloid fibrils in a rat brain model of amyloidosis (page 3, para 3). The specification also teaches that synthetic amino acids like Aib are β-sheet breaker amino acids, that when substituted in the peptide, allows the peptide to bind to amyloid polypeptides, without forming aggregation thereof (page 25, para 2). The specification further teaches that aromaticity, not hydrophobicity of aromatic amino acids "dictates amyloid self-assembly", thereby implicating the importance of aromatic amino acids (page 19, para 1). Furthermore, the specification teaches that aromatic amino acids can be natural or synthetic, and can include modificants, precursors or functional aromatic portion thereof (Table 2, page 19, para 2). Using a fluorescence assay, the specification demonstrates that the Aib-modified peptides inhibit the assembly of full length IAPP (Example 44; Figure 47). Example 45 demonstrates that dipeptides like EG16 or D-Tyr-Aib (SEQ ID NO: 121) inhibit the aggregation of IAPP peptides (Figure 48; Table 7). However, the description of dipeptides comprising L and D stereoisomers of aromatic amino acids - tyrosine, tryptophan, phenylalanine; and beta-breaker amino acids - Aib and proline, is not adequate written description of an entire

genus of dipeptides that can form an active ingredient in pharmaceutical compositions as claimed. The claims are drawn to a genus of dipeptides comprising a genus of aromatic amino acids and a genus of beta-breaker amino acids that form a genus of active ingredients in pharmaceutical compositions.

14. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The specification has not shown a relationship between the structure, function, or properties of the claimed genus of dipeptides having a genus of aromatic amino acids, a genus of beta-breakers, and pharmaceutical compositions by such. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

15. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not

"clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

16. With the exception of dipeptides comprising the L and D forms of tyrosine, tryptophan and phenylalanine, as the aromatic amino acid (or X residue), Aib and proline as the beta breaker amino acid and pharmaceutical composition comprising the same, the skilled artisan cannot envision the detailed chemical structure of all the encompassed dipeptides comprising any aromatic amino acid and any beta-breaker amino acid, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The *polypeptide itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

17. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class.

18. Therefore, only dipeptides comprising L and D stereoisomers of aromatic amino acids tyrosine, tryptophan and phenylalanine, and beta-breaker amino acids, Aib and proline, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Yamada et al. Peptide Sc 2000: 421-424, 2001.

20. The claim is drawn to a synthetic or recombinant dipeptide, comprising an amino acid sequence X-Y or Y-X, wherein X is an aromatic amino acid and Y is a beta-breaker amino acid.

21. Yamada et al. teach the enzymatic degradation of endomorphin-2 analogs on digestion with carboxypeptidase Y. The reference also teaches that degradation products include Tyr-Aib-OH or Tyr-Aib (Table 1, figure 2) (also see SCORE results – attached Appendix). Yamada et al. further teach that Aib containing analogs exhibit a longer half-life than that of endomorphin-2 on enzymatic digestion (page 422, last para). Please note

that the claim broadly reads on any dipeptide, wherein X is any aromatic amino acid that can be an L or D stereoisomer and Y is any beta breaker amino acid like Aib. Because the reference teaches a dipeptide having the structure as broadly claimed, the reference anticipates the invention.

22. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Sigma (Biochem and Reag for Life res.), page 274, 2000-2001 (listed in the IDS dated 5/11/09).

23. Sigma catalog lists an X-Y dipeptide Phe-Pro (catalog number P 6258), wherein phenylalanine is the aromatic amino acid and proline is the beta breaker. Because the reference teaches a dipeptide having the structure as broadly claimed, and because proline inherently is a beta sheet breaker, the reference anticipates the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 1, 12, 72, 77-79, 81, 95, 163 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada et al. (Peptide Sc 2000: 421-

424, 2001), in view of Friedman (J Agric Food Chem 47: 3457-3479, 1999).

25. Claims 1, 72, 74, 77-79 and 95, drawn to a synthetic or recombinant peptide, a pharmaceutical composition comprising the peptide thereof, comprising an amino acid sequence X-Y or Y-X, wherein X is an aromatic amino acid and Y is a beta-breaker amino acid. The claims further recite that 'Y' is a synthetic Cα-methylated amino acid or α-aminoisobutyric acid (Aib), and is a β-sheet breaker amino acid. The claims also recite that the dipeptide is D-Tyr-Aib or SEQ ID NO: 121.

26. The teachings of Yamada et al. are set forth above.

27. Yamada et al. do not teach pharmaceutical compositions comprising dipeptides. Yamada et al also do not teach the dipeptide corresponding to D-Tyr-Aib.

28. Friedman teaches that D-amino acids creating D-D, D-L and L-D peptide bonds make the proteolytic enzymes inaccessible to the bonds, thereby lowers the rate of hydrolysis (page 3457, para 1). Friedman also teaches that D-Tyr can be used in the treatment of diseases like hypertension (page 3468, col 2, para 2).

29. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify dipeptides comprising aromatic L-Tyr and Aib as taught by Yamada et al. to produce dipeptides comprising aromatic D-Tyr-Aib in view of Friedman.

The person of ordinary skill in the art would have been motivated to try to substitute D for L stereoisomer, because both D and L amino acids are formed due to the racemization reaction and are consumed by mammals and humans. Also, because D-amino acids form peptide bonds that are more resistant to hydrolysis, these can be used for the making of pharmacological or pharmaceutical compositions (concluding para).

The person of ordinary skill in the art would have expected because chemists have been producing dipeptides at the time the invention was made.

30. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

31. No claims are allowed.

32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

33. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory

period for reply expire later than SIX MONTHS from the date of this final action.

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

35. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

36. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
12 August 2009

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649